ELECTRODES FOR FUNCTIONAL ELECTRICAL STIMULATION

Contract #NO1-NS-6-2346

FINAL REPORT
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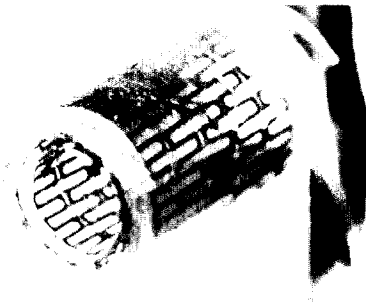
TABLE OF CONTENTS

EXECUTIVE SUMMARY



We have developed technology that will enable a user to create virtual electrodes at sites within a nerve trunk different from the actual metal contacts where current is injected. This technology diminishes the need both for a large numbers of contacts in a cuff electrode and for precise positioning of a contact in the electrode relative to a specific neural structure. This is a significant advancement for neural prostheses: it means that electrodes can be "tuned" and excitation sites can be moved, within the nerve, on a pulse-by-pulse basis. There are four features to the technology we have developed. First, a self-sizing cuff electrode enables metal contacts to be in close proximity to the axons and provides a nonconducting structure that will constrain the applied fields to the area of interest. Second, a flexible conducting structure can be assimilated in the self-sizing cuff to provide a small number of precisely positioned electrical conductors. Third, through the linear addition of electric fields (field steering), virtual excitation sites are created and moved in the radial direction around the cross section of the nerve by adding pulsed currents from two or more of the radially placed metal contacts. Fourth, utilizing the nonlinear properties of voltage gated sodium ion channels, the virtual excitation sites can be created or suppressed at positions that are deeper in the nerve by the application of a "prepulse" which preferentially alters the excitability of neurons that are larger and closest to the metal contacts.

The electrodes are fabricated using polymer-metal-polymer (PMP) technology. PMP technology employs laser machining of both silicone rubber and platinum to produce electrodes with a high degree of similarity. The PMP technology uses computer aided machining, which facilitates rapid turnaround from design to production. The fabrication process of a complete electrode assembly is simplified by requiring a lead with only four conductors and an inline connector with only four connection sites.

The self-sizing spiral cuff electrodes with four contacts were implanted on the sciatic nerve of adult cats. The cat sciatic nerve is approximately 3 mm in diameter and contains multiple fascicles of which four are motor. Utilizing field steering techniques, we demonstrated in acute experiments that any one of the four motor fascicles could be targeted and activated selectively from a very small number of motor axons to complete activation of all motor axons in the fascicle. In five animals with chronic implants, we demonstrated that time dependent field effects could be avoided by utilizing a 700 to 900 μs delay between stimuli delivered to two separate motor fascicles. Under these conditions, two motor fascicles could be activated to effect a linear addition of the response produced by each of the two motor fascicles activated separately.

Although we did not observe any functional evidence of nerve injury to the animals in these experiments, histological examination of implanted nerves continues to suggest that about one-third of the nerves mobilized and/or implanted exhibit signs of having sustained a prior insult. The signs were thinly myelinated axons, an apparent decrease in axon density, and an increase in intraneural connective tissues. Earlier studies suggest that the insult may be more

dependent on the surgical process of mobilizing the nerve than on the presence of the cuff electrode.

The results of these studies support the hypothesis that a single self-sizing spiral cuff with multiple contacts and a single lead may be used in place of several muscle-based electrodes, each with its own separate lead. The results of this study also suggest that multi-contact self-sizing spiral cuff electrodes can be used in other neural prostheses to provide selective and targeted control of axons that are bundled in trunks or fascicles (e.g. visual prostheses and auditory prostheses).

SECTION A. CLINICAL COLLABORATION

Meetings were held with both our upper extremity and our lower extremity collaborators. The focus of these meetings was to review with our collaborators the workscope of this contract award, to discuss their continuing clinical problems with electrodes, and to begin development of a plan for human feasibility testing, as is outlined in Section D of this report.

A.2: Upper Extremity

Our upper extremity collaborators have significant experience in the development and implementation of their fully implantable neuroprosthetic hand grasp system. This system has been developed over the last several decades, and utilizes intramuscular and epimysial electrodes placed in multiple sites of the arm. The collaborators are generally pleased with the success of the system and its ability to provide adequate control for the indicated functional outputs, the 2 grasp patterns of lateral and palmar prehension.

The first application for cuff electrodes looks most promising for the group of individuals with spinal cord injuries above C5, those who can not use the commercially available "FreeHand" system. A proposal has been submitted to employ cuff electrodes for the more proximal muscles of the arm, see Section D for details. A proposal was also submitted to study the feasibility of using cuff electrodes in the human to block spasticity and suppress phantom limb pain

A.3: Lower Extremity

Our collaborators working on lower extremity motor prostheses have as their long-term goal to improve the functionality and safety of lower extremity neuroprostheses for standing and walking by investigating the applicability of stimulating nerve cuff electrodes. The implanted motor system neuroprostheses currently available clinically almost exclusively utilize muscle-based (epimysial or intramuscular) stimulating electrode designs. While sufficient for basic functions in first generation neuroprostheses, these electrodes rarely recruit all of the motor units in a paralyzed muscle, especially in the large muscles of the lower extremities with complex innervation patterns and multiple motor points. Incomplete recruitment means that stimulated contractions are often barely adequate for advanced functions such as prolonged standing or stepping after paraplegia. Furthermore, several key muscles of the lower extremities are either inaccessible to muscle-based electrodes because of their geometric structure or complicated innervation patterns, which result in spillover or inadvertent activation of undesired muscles or muscle groups. Stimulating nerve cuff electrodes have been shown to be effective at completely activating motor nerves in animal models and selected organ-level human applications (respiratory pacing, bladder voiding), and can be made much more selective in their recruitment properties than muscle-based designs. They are therefore likely to maximize the forces and moments produced with FES in neuromuscular applications without spillover. Nerve cuff electrodes can also be located on major branches of the motor nerves, simultaneously solving the problem of inaccessibility of certain thin or anatomically deep muscles inherent in intramuscular or epimysial designs. See Section D for details.

SECTION B. DESIGN AND FABRICATION OF ELECTRODES, LEADS AND CONNECTORS

B.2.1: Electrode Designs

B.2.1.1: Foil-Wigglewire-Foil (FWF) Cuff Electrodes

The foil-wigglewire-foil (FWF) electrode design described in our project proposal incorporates sinusoidally curving terminal lead wires that extend from a central coiled lead cable to platinum foil disks that serve as the contact sites. This design was developed to address the problem of excessive cuff stiffness that resulted when the terminal lead segments were straight wires. The sinusoidal shape of the terminal wires should allow for increased flexibility of the resulting electrode. This has been demonstrated in pilot laboratory studies.

The following figure is the schematic used in our contract proposal and describes the original idea for the FWF electrode. The terminal lead wires were to be configured in a sinusoidal pattern (WiggleWire Lead) that extended from the electrode contact to the lead cable.

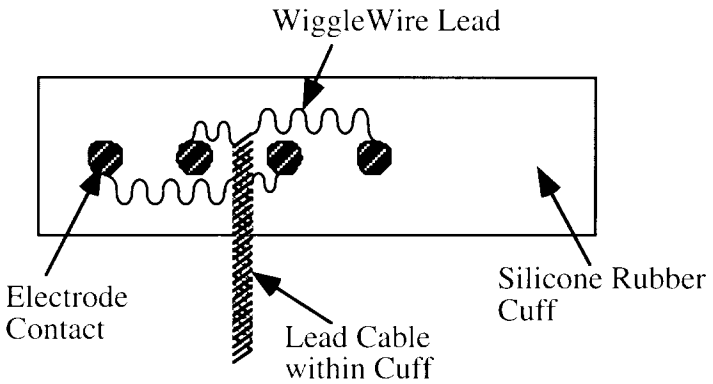


Figure B.1: Schematic of the original FWF electrode design, as presented in the project proposal. Platinum foil disks that serve as the electrode contacts, are connected to a central coiled wire lead cable by sinusoidally curving terminal lead wires (WiggleWire Lead).

As we began to consider strategies for implementing this electrode, the possibility of using a laser machining approach was raised. Due to our initial success with laser machining for the PMP electrode (as discussed in the following section), we determined that the FWF design was very compatible with laser techniques and this would in fact, be simpler than conventional machining or metal forming methods.

Conceptually, the PMP and the FWF electrode designs we arrived at are very similar in nature, although the FWF electrode is a simpler pattern design than the detailed structure of the PMP. The same fabrication methods are incorporated into the proposed methodology for the FWF design as had been established for the PMP. First, a pattern is machined into a sheet of platinum foil. This pattern defines the basic electrical pathway and creates regions of stress relief within the substrate. This piece is laminated in silicone rubber that will provide structural support during the next phase of machining. This next phase involves a series of cuts that are strategically placed so as to electrically isolate the 4 electrode pathways. After these cuts, the perimeter of the piece is machined and a second lamination process follows that creates a spiraling cuff.

Electrode Design

To implement the FWF electrode using laser machining techniques, the basic design scheme of the proposed electrode was preserved. Modifications were included to increase the structural integrity of the substrate. The modified design is depicted in the figure below.

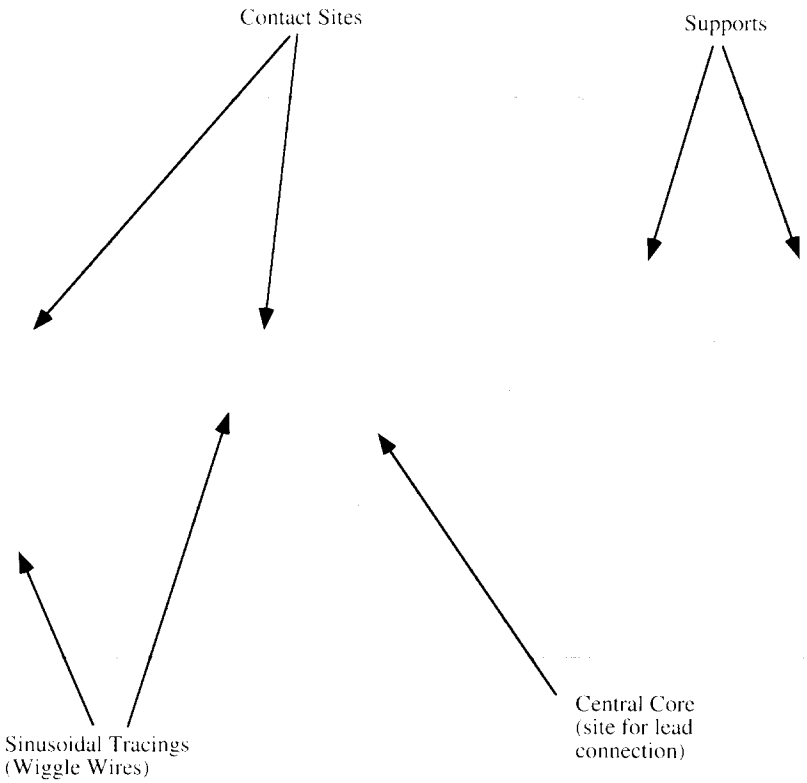


Figure B.2: Schematic of the revised FWF electrode design that was implemented using laser machining techniques. In this design, the central core, the electrode contacts, and the sinusoidal tracings are machined from a single piece of platinum foil. In the original design scheme, these elements would have been 3 separate pieces requiring welded connections.

Although the FWF electrode design is simpler to machine than the PMP electrode, we are not as confident in this electrode's mechanical reliability. In comparing the two designs, we feel that the ratio of silicone rubber to platinum in the FWF electrode is probably too high. Not enough platinum is left within the substrate to hold the structure in place when the final spiral cuff is formed. Distortion and breakage of the platinum foil tracings are indicators of this. Beyond the distortion that was evident in the design, the final cuff does not qualitatively feel as flexible or robust as the PMP.

Our experience with the FWF electrode has led us to conclude that the sinusoidal wiggle is flexible enough to allow the cuff to spiral. However, the relatively small amount of metal compared to the volume of silicone rubber and the long wavelength of the design results in some distortion and questionable mechanical stability.

B.2.1.2: Polymer-Metal foil-Polymer (PMP) Cuff Electrodes

We proposed to develop a novel technique for cuff manufacture that would improve the mechanical reliability of the cuff, as well as incorporate automated methods of manufacture. In this new technique, the basic building block of the cuff is platinum foil covered with a laser ablatable polymer, creating a polymer-metal-polymer (PMP) structure. Patterns left after cutting

through the PMP structure with a laser define the conductor pathways, the termination pads used to accommodate electrical connection to the leads, and the electrode pads that will act as conducting surfaces through which current is passed into the tissue medium.

A brief description of the fabrication steps developed for the manufacture of the PMP electrode is provided here.

Step 1: The first step in the fabrication process is for the basic structure of the electrode to be laser machined on the small sheet of platinum foil. This structure includes the traces of the paths where the current will flow, but does not yet define the four paths.
Step 2: The next step is to laminate the electrode structure. This is done using cured sheeting of silicone rubber and an elastomer which fills in the holes in the foil. This lamination stage creates a flat layer of the silicone rubber, surrounding the electrode on both sides.
Step 3: The laminated electrode is then realigned on the laser and the lead, or weld, ports are removed by the laser. This removal only consists of the lamination, the platinum foil is left intact. Laser machining is also done to isolate the conducting paths. This isolation defines the paths which the current will flow through. Lastly, the excess lamination is removed from the electrode so that only the lamination covering the platinum foil remains.
Step 4: With the lead sites exposed, the leads are then welded to the electrode.
Step 5: After the leads are attached, the final lamination takes place. A single sheet of silicone rubber is laminated to the side of the electrode opposite of the leads. This sheet is also stretched so that the lamination forms a self-sizing cuff.
Step 6: The final step in the manufacturing process is to remove the lamination from the stimulation sites. This is again done with the laser machining.

Three different designs of the PMP electrode were attempted. Each design was an improvement upon the one before, or helped to eliminate fabrication problems. The final design explored in this contract, PMP3, produced a successful self-sizing nerve cuff electrode. Throughout this contract, improvements were made in the fabrication process and in the material components of the electrode to ensure the production of a robust and accurate electrode each time. The final design is pictured below as the AutoCAD files, and a picture of a completed electrode.

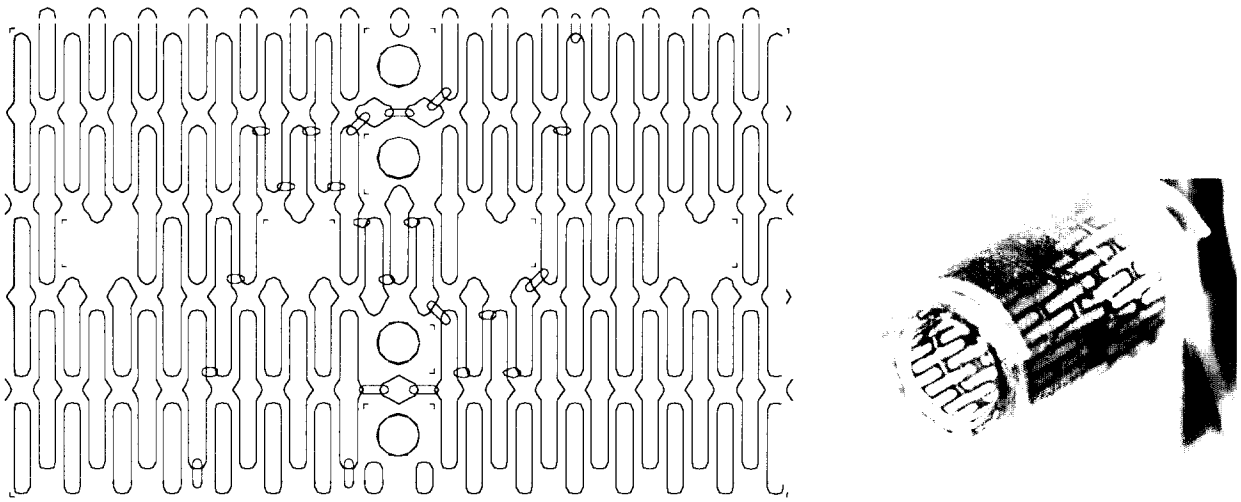


Figure B.3: On the left is a picture of all of the AutoCAD files needed to perform the laser machining of the platinum PMP3 electrode. The picture on the right is of a completed electrode in the curled state.

B.2.1.3: Characteristics of Materials used in Polymer-Metal foil-Polymer (PMP) Cuff Electrodes

Simple versions of the platinum serpentine structure were created and tensile tested. These structures were basic serpentine paths with a height of 1 mm, a thickness of 0.1 mm and a spacing of 0.2 mm. These are the same dimensions as the basic loop pattern in the current PMP electrode design. One, two and five path structures were manufactured and tested in a unlaminated and in a laminated form. The results of these tests are shown in Figures B.4 andB. 5. The data shown if Figure B.5 pertain to the stress region for manufactured electrodes (examples are indicated by arrows in Figure B.5). Data are also included for MED-4550 silicone rubber sheeting, which was used in the lamination of the structures.

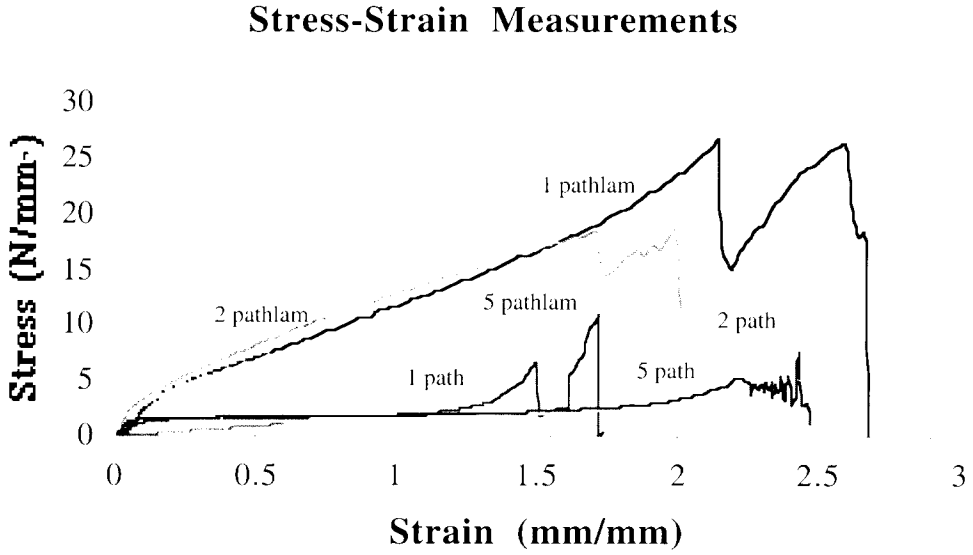


Figure B.4: Stress-Strain measurements for the materials used in the construction of P-M-P electrodes. One, two and five path serpentine were tested in the laminated and unlaminated form. A higher resolution graph, pertaining to the relevant region of stress, in shown in Figure 5.

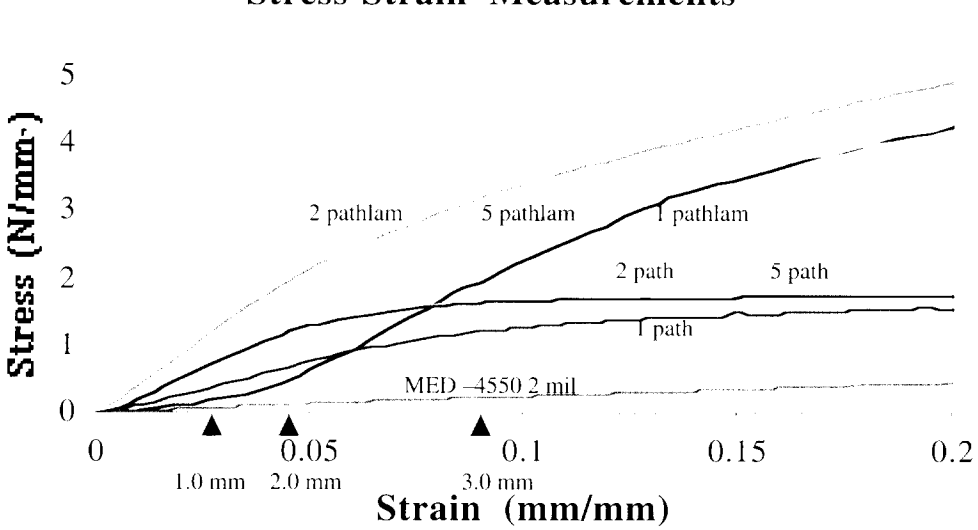


Figure B.5: Stress-Strain measurements for the materials used in the construction of P-M-P electrodes. One, two and five path serpentine were tested in the laminated and unlaminated form. Also shown in this figure are data from measurements made on the silicone rubber sheeting used to fabricate self-sizing spiral cuff electrodes using P-M-P technology. The estimated strain for a 1.0, 2.0 and 3.0 diameter cuff are indicated by the arrows.

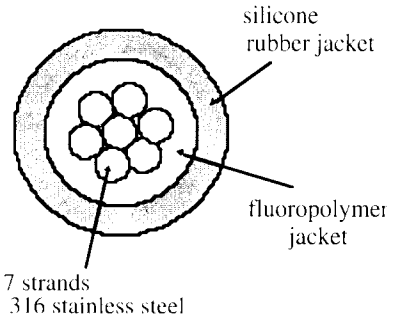
B.2.2: Lead Designs

Considerable effort has been invested in studying the lead wire for our intramuscular electrodes. Because of this wire's performance history, it has to date been adopted for use in our cuff electrodes. The wire consists of multiple strands of stainless steel insulated with a fluoropolymer coating. Fluoropolymers have been used extensively in implant devices, but generally do not bond well with other materials. For our intramuscular electrodes, this does not present a significant problem. However, in the manufacture of both spiral cuff electrodes and connectors, this non-bonding of the insulated wire is a drawback.

The spiral cuff electrodes and connectors that we investigate during this contract are made from silicone rubber and in both cases, consist of lengths of lead wire within the body of and extending beyond the silicone rubber cuff/connector. Any water or electrolyte seepage at these interfaces could promote corrosion or other modes of failure (delamination of sheeting) in the implanted electrode assembly. The poor bondability of the fluoropolymer insulation presents an increased risk of seepage at the interface and is a point of significant concern regarding the long-term reliability of these components.

In order to reduce the risks of seepage at the interface, we investigated the feasibility of applying a thin coating of silicone rubber over the fluoropolymer insulated lead wire. The top layer of silicone rubber is expected to provide better bonding to the layers of silicone rubber sheeting and elastomer in the spiral cuff and the implantable connectors molded from silicone rubber. This second insulating layer will also provide further protection of the conducting wires. We have observed that minor, local flaws in the fluoropolymer coating can go undetected by observation but can lead to significant corrosion of the underlying wire strands.

Originally, we intended to pursue having a thin, 25μm thick coating of silicone rubber insulation applied over a multi-stranded wire that is smaller than our standard size wire. This would be performed on continuous lengths of wire through a co-extrusion technique, and would result in a product with a cross-sectional profile like that depicted below.



A processor, PI Medical of Portland, Oregon, was identified and consulted for this project. Two multi-stranded wire configurations were initially shipped to PI Medical for the silicone rubber co-extrusion. These wires both consisted of 7 strands of stainless steel with a fluoropolymer jacket. The first of these was our standard size wire: 7 strands of 35μm diameter stainless steel with a 75μm jacket of fluoropolymer for a final outer diameter of 255μm. The second wire configuration is a smaller size wire: 7 strands of 20μm diameter stainless steel with a 25μm jacket of fluoropolymer for a final outer diameter of 110μm. These wires were to be coated with the PI Medical silicone rubber Silablate® MED-70 to the minimal thickness possible, expected to be 25-50μm. PI Medical was able to coat both of the wire configurations with the silicone rubber jacketing, but could only go down to a thickness of 50μm. Upon receipt of this wire, our initial evaluation involved winding the wire on a mandrel in the manner of creating a helical lead cable. We noted that the silicone rubber jacket appeared to be flaking off as the wire was wound on the mandrel. Microscopic evaluation of the coiled wire indicated that discrete sections of the silicone rubber jacket had indeed broken under the stress of winding and pulled away from the underlying fluoropolymer coating . The silicone rubber elastomer, Silablate® MED-70, has limited elongation and tensile strength, and was not appropriate for the tensile and compressive loads that are placed on the coiled wire lead cables.

We again consulted PI Medical and because of the limited physical properties of their elastomers, they decided to use another silicone rubber product for the co-extrusion. A liquid silicone rubber formulation from NuSil Silicone Technologies, MED-4950, was chosen for its ultra high tear strength, elongation, and tensile properties. Fifty feet of a slightly different wire configuration was sent to PI Medical for the co-extrusion. This wire consisted of 7 strands of 35μm diameter stainless steel, but with only a 50μm jacket of fluoropolymer, for a final outer diameter of 205μm. PI Medical was able to process this wire and apply a 50μm coating of silicone rubber. It was noted that the silicone rubber jacket, like the silicone rubber sheeting we have previously investigated, is 'sticky'. The wire adhered to itself and to the mandrel upon winding, requiring significant effort to remove the mandrel and leading to a distorted and damaged lead cable. Surfactant coating (Liquinox® cleaner) applied to the wire and the mandrel helped to reduce this stickiness, but was not entirely effective.

In addition to our efforts working with PI Medical, we investigated alternative sources and approaches for the silicone rubber coating of our lead wires. Specialty Silicone Fabricators, the company that processes our silicone rubber sheeting, was contacted regarding this project. Specialty Silicone Fabricators has had prior experience applying layers of silicone rubber over fluoropolymer and provided some advice on how to best approach this project. First, they recommend that a surface treatment be applied to the fluoropolymer in order to improve the bondability of the fluoropolymer with the silicone rubber. The two materials will not chemically bond, but a roughened fluoropolymer surface will improve the mechanical bonding between the two materials. The roughening of the fluoropolymer can be done through a chemical etchant solution, like Tetra-Etch, or can be done through a corona etch, where the material is exposed to a high frequency voltage. We have identified a source for continuous length corona etching of our wire, as the chemical etchants are more amenable to batch processing and require and generate toxic substances. To apply the silicone rubber, Specialty Silicone Fabricators states that either a dip coating or a co-extrusion process be employed. The dip coating process could likely result in a thinner overall jacket of silicone rubber, on the order of 25μm. However, dip coating is a batch process and would not be appropriate for continuous lengths of wire. Using a co-extrusion technique, the minimal applied thickness of silicone rubber would likely be 50μm, but the process could be performed on continuous lengths of wire.

Specialty Silicone Fabricators was able to co-extrude 75μm of MED-4750 (a Nusil gumstock)silicone over 1x7x0.0008 inch stainless steel wire with 50μm of PFA coating. Testing of the silicone rubber overcoated wire revealed that this wire would be appropriate for use in electrode fabrication. However, it is desired to minimize the thickness of the wire since four wires will be wound together in the PMP fabrication process. An attempt was made by Specialty Silicone Fabricators to extrude just 50μm of MED-4750 over 1x7x0.0008 inch wire with only 25μm of PFA. This effort was unsuccessful due to a variance in tensile strength in the stainless steel wire. It is believed by Specialty Silicone Fabricators that they can extrude 50μm of the MED-4750 silicone over a thinner wire, but the tensile strength must be equivalent or higher to the original wire batch that was successful.

B.2.3 Connector Design

In the contract, we proposed to incorporate the miniature pin and socket in-line connector design developed by PI Medical into our cuff electrode assembly. Previous studies that investigated the interface between this connector and the fluoropolymer-coated lead showed leaking over time. It was expected that the incorporation of the silicone rubber overcoated leads described in section B.2.2 would help eliminate the leakage. Due to the difficulties in

successfully manufacturing a silicone overcoating of the appropriate thickness, the connector interface was not revisited during this contract.

B.2.4.1 Silicone Rubber Sheeting

The goal of this project was to establish performance specifications for the silicone rubber sheeting used in the spiral cuff electrode fabrication. Tests were conducted to determine the mechanical and physical properties of four different silicone rub ber sheeting formulations. Additionally, we investigated the effects of aging and sterilization on these properties. All specimens tested had a thickness of 0.002inch (50μm). The control sample was supplied by Dow Corning and manufactured by AVECOR (Q7-4550.) This sheeting was used in the manufacture of our previous cuffs, but can no longer be used since it is not approved for long-term human implants. The new formulations are MED-4550, MED2-6640, and MED2-6641-1 and are supplied by NuSil and manufactured by Specialty Silicone Fabricators.

Samples from each sheeting formulation were put into three experimental groups – aged, sterilized, and control. Each sample was cleaned according to the cleaning protocol in QPR# 4 (N01-NS-0-2395.) The aged group consisted of ten samples of each sheeting formulation which were placed in a saline bath at an elevated temperature to simulate five years aging in the body. The specimens were kept in the bath for 32 hours at 82°C. The sterilized group consisted of ten samples of each formulation that underwent ethylene oxide (EO) sterilization. The control group consisted of ten samples from each formulation which were not put through any processing.

The first test each specimen underwent was a surface observation. The specimens were examined under a microscope to determine their surface properties. Moreover, their surface descriptions were recorded. The next test the silicone rubber sheeting specimens underwent was a measure of their contact angle. A contact angle goniometer was used to measure the advancing and receding water contact angles of each sample. These contact angles characterized the hydrophobicity or hydrophilicity of the sheeting, which gives us an indication of the "stickiness" of the surfaces. The specimens then underwent friction testing. The friction of each sample was measured using a coefficient of friction testing fixture, which was connected to a tensile testing machine. The coefficient of friction for a silicone rubber to silicone rubber interaction is determined from this test. The final test performed was the tensile test, which determined the modulus of elasticity, the ultimate tensile strength, the percent elongation, and the yield strength of each specimen. The results from these tests are shown in the figures below for the control group. The data for the aged and sterilized groups can be seen in progress reports 7 and 8, but are not shown here because there was little to no variance between the three groups.

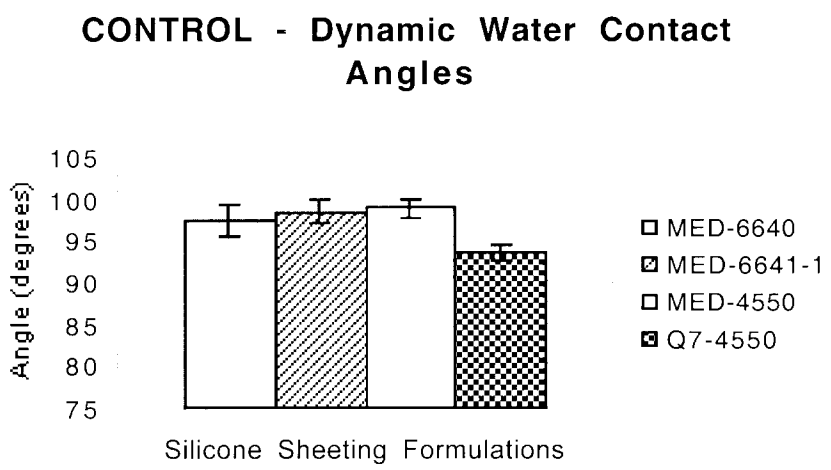


Figure B.6: The bar chart above represents the averages of the advancing angles for the 4 silicone sheeting formulations tested.

The MED2-6641-1 consistently has the highest advancing angle for each group, which means that it is the most hydrophobic of the formulations. The MED-4550 is a replication of the Q7-4550 formulation, so it was expected that these formulations would have similar properties. Instead, the MED-4550 actually becomes more hydrophilic with aging and sterilization. The Q7-4550 was, on average, the most hydrophilic of the formulations tested.

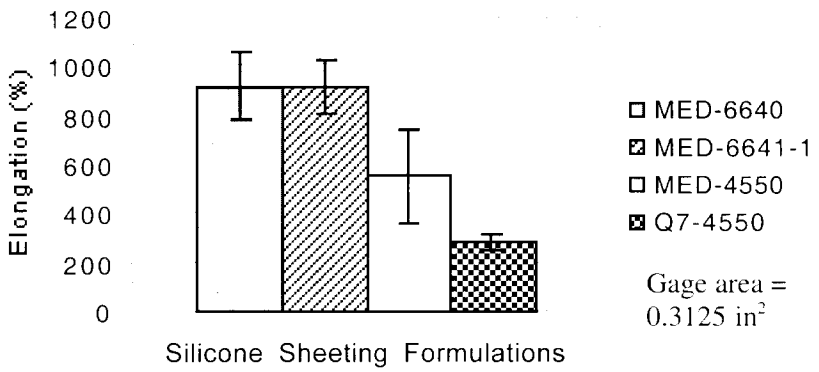


Figure B.7: The bar chart above represents the amount that each formulation will elongate before failure. This elongation is shown as a percentage of its original gage length.

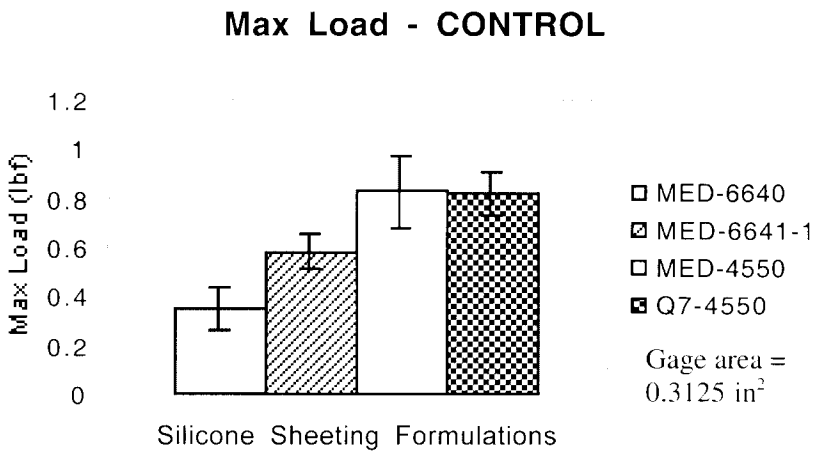


Figure B.8: The maximum loads that the silicone sheeting samples were able to withstand before failure are presented in the bar chart above. This bar chart contains the data for the control groups.

Those materials that have a very high percent elongation consequently have a very low maximum load. Specifically, MED2-6640 and MED2-6641-1 had high percent elongation's, while MED-4550 and Q7-4550 and the highest maximum loads.

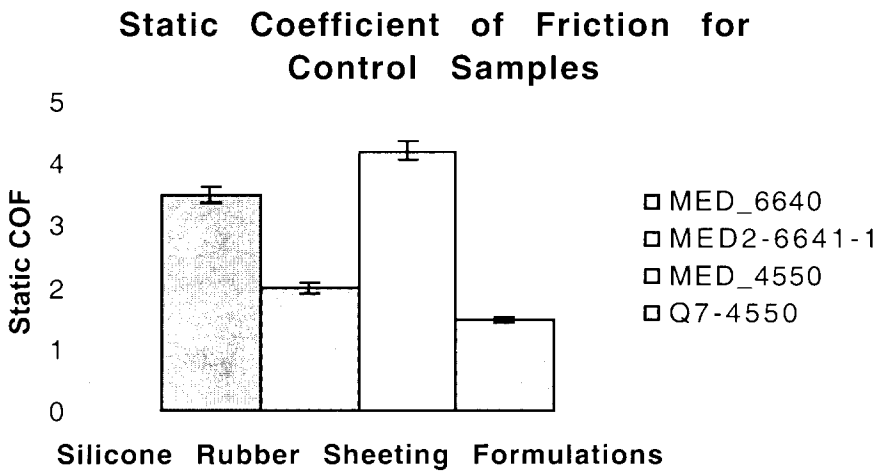


Figure B.9: The average coefficient of friction found for each silicone sheeting formulation tested is shown in the bar chart above. This chart consists of the results for the control groups.

It can be seen that the Q7-4550 and MED2-6641-1 formulations consistently had the lowest coefficient of friction, while the MED2-6640 and MED-4550 consistently had the highest. After studying the data shown above, it was realized that no one formulation tested rates the highest in the characteristics desired for this application. Currently, we are using MED-4550 silicone rubber sheeting for the fabrication of our electrodes.

Diameter Relaxation Test

In order to determine if the silicone sheeting "relaxed" or moved during aging, silicone rubber cuffs were placed in a temperature bath and any change in diameter was observed over a 28-day period. Specifically, cuffs were placed in five different flasks (eight samples from one cuff lamination per flask). The flasks contained phosphate buffered saline solution and were sealed with a rubber stopper. The rubber stoppers had inlet and outlet ports for gas flow to be bubbled through continuously. The gas mixture used was 2% O and 5% CO_2 in N. The five flasks were placed in a water bath held at 85°C.

The diameters of each cuff were measured and recorded using a microscope and a gradicule at 0,7,14,21,and 28 days. The diameters were measured "wet" and "dry". The cuffs were considered "wet" when they had absorbed 0.4% of their initial mass, per data obtained from Avecor, Inc. This mass was reached after being soaked in Ultrapure water at room temp for 15 minutes. The cuffs were considered "dry" after sitting in a dessicator with a vacuum for 15 minutes (i.e. the extra 0.4% mass of water was removed).

The data were analyzed for wet and dry measurements over the 28-day period. The chart below contains the average diameters and their standard deviations for all of the cuffs tested at the five measurement intervals.

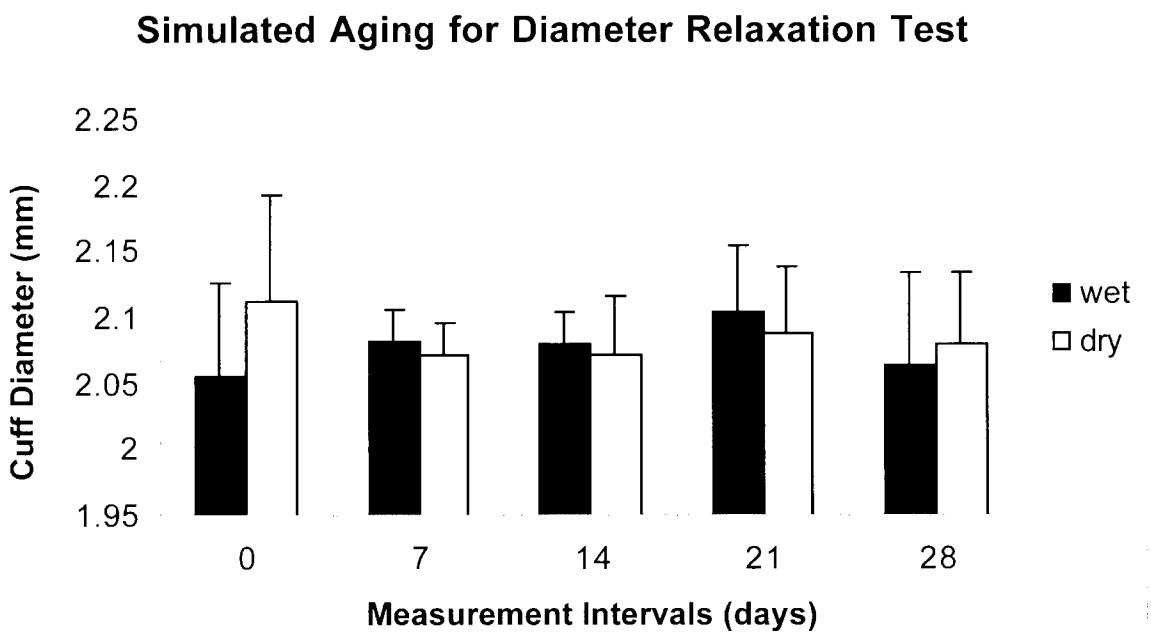


Figure B.10: Averages and standard deviations for the diameters of the silicone rubber cuffs over the 28-day simulated aging period.

It was found that there was no statistically significant change in the diameters of the cuffs over the 28-day period. There is also no statistical difference between measuring the cuffs wet and measuring them dry.

B.2.4.2: Weld Strength

Before welding could begin on this PMP electrode, a welding method had to be devised which would allow for current to pass through the small window opening in the lamination for the weld to occur. This involved building a new welding table that allows for a point contact on both the top and bottom of the electrode. The lamination prohibits using the flat copper table since current does not pass through the silicone rubber, and the lamination prevents platinum from touching the table. A schematic of the new weld table is shown below.

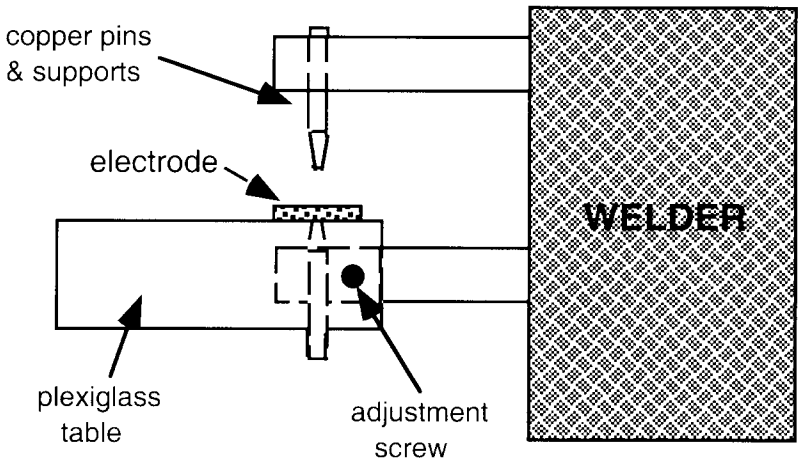


Figure B.11: This figure is a simple model of the weld table that was built to weld on the PMP2 electrode. The pin from the bottom is embedded in the table with a setscrew from the other side. It can also be adjusted for height so that the pin just touches the platinum which is approximately 100 microns from the surface of the table due to the lamination. This weld process should be able to weld on any future electrodes created because of its adjustability.

With this method developed, an effort was made to determine the best weld settings for this electrode. A range of currents from 0.6mA to 1.2mA and forces ranging from 30 to 50 ounces were used to determine the strongest weld. Wires were welded using the different combinations and then tensile tested. It was found that the strongest range on welds was around 0.8 and 1.0mA with forces at 30, 40, and 50 ounces. More samples were made within this narrowed range and tensile tests were again performed. This testing revealed that 1.0mA and 50 ounces result in the strongest weld. At this setting the wire reaches its ultimate tensile strength before the weld.

With the weld settings determined, testing to determine the strength of the weld after lamination and simulated aging was done. Three different groups of welds were tensile tested to failure. The first group was a control group that was a weld in the contact window of laminated platinum. The second group was pressed; meaning the weld was laminated and put in a heated press for 1 hour at 2 tons and 205°F. The last group was aged, after being pressed the laminated welds were soaked in an elevated temperature saline bath to simulate 5 years *in vivo*. The control group had an average peak load of 0.13597 N (SD=0.07146 , n=9). The pressed group could sustain an average peak load of 0.24525 N (SD=0.07835, n10) and the aged group could sustain an average peak load of 0.28809 N (SD=0.02293, n10).

The yield strength of the laminated and the aged groups were greater than the yield strength of the control group. The differences were statistically significant at the 99.5%

confidence level (Students "t" test, assuming the variances are unknown and unequal for each population tested). The difference between the yield strengths of the pressed and aged groups was not found to be significant at the 95% confidence level.

Microscopic examination of the welds after tensile testing revealed that wire adjacent to the weld site was failing rather than the weld itself. Under normal conditions, the breaking load of the wire is approximately 4.5 N, which is much higher than the breaking load of the wire in this testing. We interpret this difference to mean that the wire was weakened at the weld. Considering the yield strength measurements for the welded, laminated and aged groups along side the breaking strength of the wire, we concluded; 1) that the welding process reduces the strength of the wire at the site of the weld, 2) that the effect of the lamination process is to distribute some of the applied load to the non-welded parts of the assembly, and 3) that the simulated aging does not alter the weld strength.

B.2.4.3: Contact Window

Previous methods used to fabricate contact windows employed a metal cannula to open "windows" in the silicone rubber surface of the PMP structure. Microscopic examination of the platinum underlying the "window" revealed that the foil was often damaged by this procedure. It was proposed in the contract proposal that this procedure be studied and modified to ensure that an accurate and non-damaging "window" was made.

In developing this PMP electrode, it was discovered that the laser used to cut the platinum foil could also be used to remove the silicone rubber on the contact sites. This has been done, and is a much more precise method. The contact windows are always cut to 0.5mm in diameter, and the laser does not damages the foil. The only possibility for damage from this procedure is the process of removing the silicone rubber pad after the laser cut is made. Currently, these pads are removed with forceps. This method has the possibility of scratching the platinum with the forceps tip. These scratches have not been found to cause any functional damage to the electrode.

B.2.4.4 Mechanical Failure Mode of Completed Electrodes

In the contract, we proposed tensile testing the completed electrode to failure with axial tension. It has since been decided that this is not a realistic form of failure for the spiral cuff electrode. The electrode does not undergo excessive axial tension, and if at any point it did, it is believed that the nerve would be damaged much earlier than the cuff would fail. The likely failure due to tension would be the breakage of the lead or weld due to tethering of the leads. This form of failure was tested with the weld strength testing performed and reported in Period 6. The tensile testing of the electrode was therefore not performed in this contract.

B.2.4.5: Cleaning Protocol

The cleaning procedure we have used in the past on the spiral cuff electrodes involves multiple days of soaking in solutions of soapy water, ethanol, and pure water. This process is time consuming. The cleaning process, was studied during this contract in order to improve the efficiency of the process without compromising the quality of cleaned product.

The cleaning protocols that were studied were the past protocol for spiral cuff electrodes, the current protocol for intramuscular electrodes, and a new method that is a combination of the two methods. A control group, uncleaned electrodes, was also included in the study. All three cleaning protocols employ the use of the ultrasonic cleaner, Liquinox® (Alconox, Inc.), ethanol (reagent grade, Fisher Scientific), and ultrapure water (Milli-Q, Millipore). The only variations are time and soaking versus ultrasonic cleaning. The samples used to test the different processes

were made without the platinum or lead wires. They were manufactured with a layer of silicone rubber stretched to a calculated value that yielded cuffs of a 3mm diameter. They were cut out of a sheet of the silicone rubber to have a cylindrical height of 6mm. The cuffs were cut to be a length that was equal to two wraps of the silicone rubber around itself. These samples were then cleaned according to a given protocol and then each was studied using electron microscopy.

The samples cleaned with the shortened, new method met or exceeded the results from previous testing with the old method. Some of the factors that lead to this improvement are believed to be opening the cuff in the pure LiquiNox, the ultrapure water rinses after sonification, and the addition of heat to the process. The steps of the new method are listed below.

Spiral Cuff Electrode Cleaning Protocol (new method):

1. Dip the electrode in pure Liquinox® solution and separate the cuff layers to allow penetration of the solution into the cuffs.
2. Sonicate the electrode in a 1:100 solution of Liquinox® in ultrapure water for 10 minutes with the heat function on the ultrasonic cleaner turned on.
3. Rinse the electrode in ultrapure water 5 times.
4. Sonicate the electrode in ultrapure water for 5 minutes.
5. Sonicate the electrode in 95% ethanol for 5 minutes.
6. Rinse the electrode with ultrapure water 5 times.
7. Sonicate the electrode with ultrapure water for 5 minutes.
8. Allow the electrode to dry on the clean room wiper.
9. Package the electrode for sterilization.

This method is believed to be the best combination of effectiveness and efficiency and is currently used as the spiral cuff electrode cleaning protocol.

B.2.5.1 Flexion Testing

In the contract, we proposed a flexion test that would piston the electrode up and down using a localized force for 5 million cycles. Although an *in vivo* electrode might undergo some point flexion due to nearby muscle flexion, the flexion would most likely be a distributed pressure on the nerve and electrode. The proposed test would therefore not be a reasonable mode of failure. The 5 million cycles would also be excessive considering what the electrode would undergo. It was decided that this test would not be performed in lieu of two new tests that better represent the actions the cuff undergoes.

One of the tests performed was a rolling test. This test was developed in order to determine whether the electrode would incur breaks and/or lose its conductivity after being opened 100 times. It was estimated that an average electrode would be opened completely, and held flat, no more than 10 times during manufacture, cleaning, and implant. Five electrodes were opened and closed 100 times. This allows for a safety factor of 10. Every 10 cycles, the resistances between the contact and the leads were measured. The data from the resistance measurements were analyzed and interpreted to indicate that there was no significant increase in the resistances of the electrodes over the 100 cycles. An increase in resistance would have indicated a crack or break in the platinum conduction paths. All of the electrodes were examined using microscopy after the testing was complete. No breaks were detected in the platinum of any of the electrodes. Scanning electron microscopy was performed on the stimulation sites of three of the electrodes to determine if any damage was caused by taking the resistance measurement.

The microscopy revealed no damage on the stimulation sites other than scrapes occurring from site removal.

The second flexion test performed involved the study of the electrode lamination after being aged *in vitro*. Four sets of 8 cuffs were placed in four 250 mL flasks containing a phosphate buffered saline solution held at 85°C for 28 days. Each cuff is 4 mm in width and at least 10 mm in length. A gas mixture of 2% O, 5% CO_2, and 93% N was continuously bubbled through the flasks. The flasks were set on a hot plate/stirrer. A 3.6 cm magnetic stirrer bar with a 1 cm diameter was placed in each flask and stirred so that the solution formed a vortex approximately 60 mL deep. After a 28-day period, the cuffs were removed and tensile tested to failure. The gage length of the cuffs was 8 mm. Control cuffs, which were not aged, were also tensile tested. The tensile curves for the cuffs in each set were averaged to obtain average data points which form a tensile curve for each set (2 control sets and 4 aged sets). The first linear region of the curves was studied to determine the spring constant.

The spring constants were found for the two groups of cuffs, aged and control. The spring constants (k) were found by taking the k's for each tensile curve and averaging them. The spring constant for the aged group of cuffs was found to be 0.2514 N/mm^2 and the spring constant for the control set is 0.2458 N/mm^2. A student's t-test assuming equal variances and a null hypothesis that the means are equal was performed on these two data arrays and revealed an alpha of 0.6237 for a two-tailed probability distribution, which means that we cannot claim that the two spring constants are statistically different. Another student's t-test was then performed on the data after adding one standard deviation to the control set. This test produced an alpha of 0.0146. This can be interpreted to mean that the two spring constants are within one standard deviation of one another. We conclude that there was no significant measurable change in the tensile properties of the silicone rubber cuffs after 28 days of simulated accelerated aging and mechanical movement.

Four PMP3 electrodes were also aged in flasks at 85°C for 28 days on a hot plate/stirrer. These electrodes were inspected using visual microscopy. No delamination or damage was observed. The electrodes were also used in the corrosion testing project (Section B.2.5.2). Once the stimulation was finished, the electrodes were examined using light microscopy and Scanning Electron Microscopy (SEM). No noticable difference was observed between the stimulated and control sites.

B.2.5.2 Corrosion Testing

Two sets of four electrodes were tested for corrosion. One set contained electrodes that underwent simulated aging. These are the four electrodes tested in the Simulated Aging/ Flexion test of Section B.2.5.1. The other set contained two electrodes that were used in the rolling test (Section B.2.5.1). These samples represent electrodes that have been flexed beyond what is expected during manufacture and implant. The remaining two samples were unused, meaning they had not been flexed, aged, or tested since manufacture.

The stimulation involved four electrodes (sets of two running in parallel) pulsed at the maximum expected stimulus parameters. Specifically, they were pulsed continuously at 20 Hz with biphasic, charge balanced, capacitive coupled, rectangular waveform at 3 mA with 10μs pulsewidth and 0 interphase delay. The second batch of electrodes were stimulated in the same way, except using a 30Hz frequency and a 5mA current. One electrode (4 contacts) received 3 anodic currents and 1 random control (no pulsing). The second electrode received 3 cathodic currents and 1 random control. The resulting voltage between each electrode contact and a saturated calomel reference electrode was measured using high input impedance (10^{12} Ω) buffer amplitudes and an RMs voltmeter. These measurements were taken twice each week. The test

was run in a bath of phosphate buffered saline solution. A gas mixture of 2% Oxygen, 5% Carbon Dioxide, and 93% Nitrogen was continuously bubbled through the flasks. The set-up for the test was shown in progress report #10.

The amount of platinum in solution was tested before the test began and after the 28 day period. SEM was performed on a control group of three electrodes (12 stimulation sites) that were not tested. Microscope inspection and SEM were also performed on the stimulation sites of the tested electrodes (32 sites) and on any suspected corrosion sites. This evaluation took place after the 28-day test period. Deposits on the electrode contacts were also examined for elemental composition using EDAX. The electrodes were also examined for delamination.

Visual and scanning electron microscopy were also performed on the stimulation sites of the electrode to compare the stimulation sites after stimulation with the control pictures taken of sites that had not been stimulated. There were no noticeable changes in the stimulation site pictures between the control and stimulated sites.

Potential measurements were taken for each stimulation site every three to four days during the 28-day test. The electrode potential, during the interpulse interval, averaged between 30 and 40 mV(SCE) during the 28-day test period.

The first set of four electrodes (two unused and two from the rolling test) completed the 28 day stimulation.

The amount of platinum in the phosphate buffered saline solution was also measured before and after the 28-day period. The carbon fiber electrodes were also tested for platinum at the end of the 28-day test. No platinum was detected in the baseline samples. There was also no platinum detected in the 28-day samples. The detection limit for platinum was 0.1 μg per mL of solution. These results were interpreted to indicate that if corrosion occurred during the 28-day period it was below our detection limits.

In order to predict the life of this electrode, it is useful to consider a typical stimulus regime for a prosthetic device. Estimates of hand grasp prosthesis use report that the system requires 200,000 pulses per day, totaling 365 million pulses over a five-year period. The PMP electrodes tested were stimulated at a rate of 20 pulses per second over a 28-day period. This equates to 48,384,000 pulses delivered to each contact stimulated. Three contacts were stimulated per electrode which, when added, equals 145,152,000 pulses. Because there was no loss of platinum, within the detection limit, it is reasonable to say that the electrode should last at least 2 years.

B.2.6 In Vivo Testing

The *in vivo* testing was performed on three PMP electrodes implanted in cats for 9 months each. Two PMP2 electrodes were implanted. These electrodes were explanted between one and two months after implant due to suspected electrode failures. Upon explant, the electrodes were evaluated using light microscopy and their resistances were recorded. These measurements are shown in Table B.2.6.

Table B.2.6

Electrodes Used in In Vivo Testing									
Type Size Date Number	WW	WW 2.7 4/30/1998 1/2/2006	PMP2 2.6 7/23/1998 6of6	PMP2 3.0 7/23/1998 2of6	PMP2 2.8 7/23/1998 5of6	WW 3.0 4/30/1998 1/2/2006	PMP3 2.8 11/23/1998 1of4	PMP3 2.8 11/17/1998 2of2	PMP3 3.0 11/17/1998 1of2
Cat#	380	399	545	535	552	553	555	576	569
Implant Date	5/20/1998	6/24/1998	7/29/1998	9/1/1998	9/15/1998	11/10/1998	12/3/1998	12/8/1998	12/16/1998
Implant Duration (days)	49	428	0	43	30	289	257	252	244
Resistances-1			370	406	400		506	486	486
2			370	404	401		507	480	482
3			370	405	400		505	478	510
4			372	412	400		503	488	484
Explant Date	7/8/1998	8/26/1999	7/29/1998	10/14/1998	10/15/1998	8/26/1999	8/17/1999	8/17/1999	8/17/1999
Resistances-1				503	X		505	457	X
2				528	424		503	442	484
3				376	411		501	439	474
4				369	378		503	438	475
Comments			cleaned & resterilized		break near contact#1			nerve dia =2.55mm	nerve dia =2.8mm

Note: Resistances taken from lead to contact of electrode(before and after in vivo).

The primary observation from these impedance measurements is that the lead to contact resistance is in the range of 500 ohms and remains stable over a nine month implant period.

B.2.7 "Accelerated" Aging

Although this section was not originally proposed in the contract, an article on accelerated aging of polymers for shelf-life made us wonder if our current model used for predicting life in vivo may not be accurate for our application. A research study was launched to investigate "accelerated" aging models.

Polymer performance is directly related to how its structure, and therefore mechanical properties, change with time. It is desired to find a relationship between the time a polymer is in use, or stored, and the temperature at which it is used or stored at. This relationship would allow for an accurate way to perform accelerated aging tests. In other words, a polymer could be raised to an accelerated temperature over a short period of time in order to simulate the aging it would see over a longer period of time.

We at the Applied Neural Control Laboratory at Case Western Reserve University have been searching for ways to estimate if our electrodes will "hold up" inside the body for a given number of years. We would like to be able to tell any interested party what the life expectancy of our electrode is. Currently, the only accurate way of measuring electrode life is to implant the electrode *in vivo* and determine when it fails. This process could take many years. Improved devices and material changes are occurring rapidly in the field of biomedical engineering. Because of this, it is necessary to accelerate the aging process so that a life expectancy estimate can be made within a more timely period, such as a few months. Such accelerated aging processes have been performed previously by increasing the temperature that the specimen is held at. In order to make such an estimate, a relationship between time and temperature appropriate for polymers must be found.

Researching temperature accelerated aging revealed three categories of methods that have been used, or are suggested to be used for the "accelerated" aging of polymers. These models are the Larsen-Miller model, Arrhenius based models developed by Hemmerich, NAMSA, and Edel, and a model to develop a relationship unique to an application referred to as the D&A model. These models were discussed in PR#10. Some of the models suggested an upper limit of 60°C so the models were compared at 60 and 85°C.

Table B.1: Comparison of Accelerated Aging Models at 60°C and 85°C for 28 days

Model	Author, Year	Accelerated Aging		Predicted Aging	
		Temp (C)	Time(days)	Time(days)	Time(years)
Creep	Larsen&Miller, 1952	60	28	1101.5	3.02
Arrhenius Based	Hemmerich, 1998	60	28	129.2	0.35
	NAMSA, 1998	60	28	138.5	0.38
	David Edel, 1998	60	28	371.6	1.02
D&A	Donohue&Apostolou, 1990	60	28	N/A	N/A
Creep	Larsen&Miller, 1952	85	28	59055.0	161.80
Arrhenius Based	Hemmerich, 1998	85	28	269.1	0.74
	NAMSA, 1998	85	28	783.3	2.15
	David Edel, 1998	85	28	4236.2	11.61
D&A	Donohue&Apostolou, 1990	85	28	N/A	N/A

We have chosen a test set-up for aging at 85°C for 28 days. According to the Hemmerich model this would only simulate 0.74 years. According to the Larsen-Miller model, this simulates 161.8 years. Therefore, we believe that the polymers that are tested using the above parameters, are being aged somewhere between 28 days and 161.8 years.

SECTION C. *IN VIVO* EVALUATION OF ELECTRODES

C.1 Comparison of the Recruitment Characteristics for Monopolar and Tripolar Self-Sizing Spiral Cuff Electrodes

Using a self-sizing spiral cuff electrode placed on the sciatic nerve of cat, the joint torque evoked with stimulation applied to contacts in a monopolar configuration was judged to be the same as the torque evoked by stimulation applied to contacts in a tripolar configuration. Experiments were carried out in six acute cat preparations. In each experiment a twelve contact electrode was placed on the sciatic nerve and used to effect both the monopolar and tripolar electrode configurations. The ankle torque produced by electrically evoked isometric muscle contraction was measured in three dimensions: plantar flexion, internal rotation and inversion. Based on the recorded ankle torque, qualitative and quantitative comparisons were performed to determine if any significant difference existed in the pattern or order in which motor nerve fibers were recruited. No significant difference was found at a 98% confidence interval in either the recruitment properties or the repeatability of the monopolar and tripolar configurations. Further, in the course of these experiments, isolated stimulation of single fascicles was observed. Once fibers in one fascicle were activated, recruitment of that fascicle was modulated over the full range before "spill-over" excitation occurred in neighboring fascicles. These results indicate that a four contact, monopolar nerve cuff electrode is a viable substitute for a twelve contact, tripolar nerve cuff electrode. The results of this study are also consistent with the hypothesis that multi-

contact self-sizing spiral cuff electrodes can be used in motor prostheses to provide selective control of many muscles. Typical recruitment curves are shown in Figure C.1.1.

Comparison of Monopolar (solid) and Tripolar (open) Configurations in Cat# 092

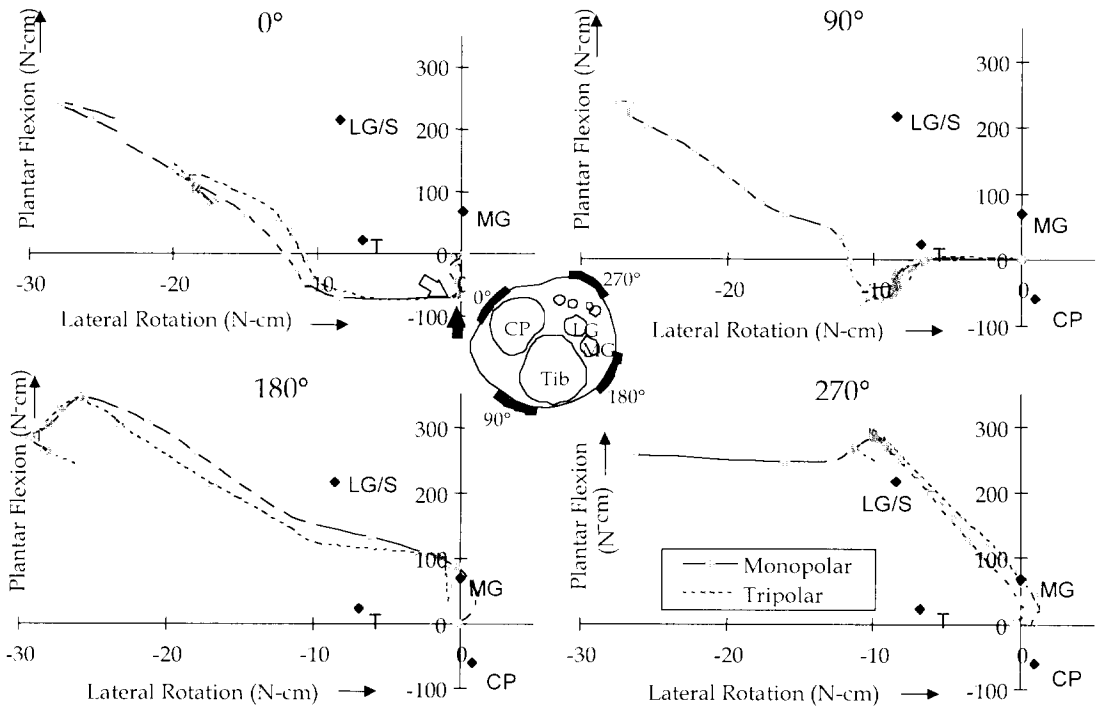


Figure C1.1 - Monopolar and tripolar torque output achieved at the 0°, 90°, 180° and 270° contacts in cat #092 shown with plantar flexion plotted against lateral rotation. The monopolar recruitment curves are shown with solid data points while the tripolar recruitment curves are shown with open data points. Full recruitment of each individual fascicle is shown by the corresponding diamond: medial gastrocnemius (MG), lateral gastrocnemius/ soleus (LG/S), tibial (T), common peroneal (CP). The physical relationship between the electrode and each fascicle within the nerve are illustrated by the inset figure of the nerve cross section.

C.2 Selective and Controlled Activation of Any One of Four Motor Fascicles in the Cat Sciatic Nerve

We have demonstrated that any one of the four motor nerves in the cat sciatic nerve could be activated selectively, from threshold to saturation, with a self-sizing spiral cuff electrode containing four radially placed monopolar contacts. In the thirty-six experiments carried out, twenty-three fascicles could be activated selectively with current stimuli applied to a single contact and in ten of the remaining experiments stimuli were applied to two contacts "field steering" to effect selective activation. In three experiments time constraints precluded attempting selective activation through "field steering" techniques. In eight of the ten cases where "field steering" was used a positive and a negative current source (anodic steering) were required to achieve the desired fascicle and in the remaining two cases two negative current sources (cathodic steering) were required. The location of electrode contacts was well correlated to the close proximity of the contacts to the target fascicle. In 7 of 8 experiments, carried out in two animals, selective activation was verified by collision block techniques. The results of these experiments support the hypothesis that selective and independent activation of any

of four motor fascicles in the cat sciatic is possible using a four contact self-sizing spiral cuff electrode. A summary of these data are shown in Table C.1.

Cat #	Medial Gastrocnemius				Soleus/Lateral Gastrocnemius				Common Peroneal				Tibial			
	0	90	180	270	0	90	180	270	0	90	180	270	0	90	180	270
244	-	o	o	o	o	o	-	o	o	-	o	o	-	o	o	+
256	o	-	+	o	-	o	o	o	o	o	o	-	•	•	•	•
262	o	o	o	-	•	•	•	•	o	+	-	o	o	-	o	o
300	-	o	o	-	o	o	o	-	o	o	-	o	•	•	•	•
303	o	-	-	o	o	o	-	o	o	o	-	o	o	-	o	o
302	o	o	-	+	o	-	o	o	-	o	o	o	o	+	-	o
363	o	o	o	-	-	o	o	o	o	-	o	o	o	o	-	o
388	o	-	o	o	o	o	-	o	+	o	o	-	-	o	o	o
383	-	o	o	o	o	-	o	o	o	o	-	+	o	o	+	-

Table C.2.1 – Shown in this table are the stimulation combinations used at the level of the sciatic nerve to achieve the same torque output as each corresponding fascicle for each experiment. For each case in which the same torque output was achieved, four placeholders were entered to represent how the four corresponding contacts (0°, 90°, 180° and 270°) were used. An open circle (o) represents a contact that was not used for that particular configuration. A minus sign (-) indicates that the corresponding contact was pulsed in the cathodic direction. A plus sign (+) indicates that the corresponding contact was pulsed in the anodic direction. Four filled circles (• • • •) indicate that the particular torque was not achieved fully with single contact stimulation but not targeted using steering currents due to time limitations. In no case was a particular torque not achieved when multiple contact stimulation was attempted. The shaded cells are the cases in which "collision block addition" was used to verify the corresponding fascicle was fully and selectively activated.

C.3 Linear Summation of Torque Produced by Selective Activation of Two Motor Fascicles

Linear summation of torque, produced by selectivate activation of two motor fascicles in the cat sciatic nerve, was achieved using a four contact self-sizing spiral cuff electrode. To effect a linear summation of torque it was necessary to separate the two stimuli by at least 700μsec in time. Using a 900μsec delay between pulses, linear summation of two different torque outputs was successfully achieved in 125 out of 129 trials across five cats. The animals had cuff electrodes in place for periods ranging from 252 to 428 days. The results of these studies support the hypothesis that a single self-sizing spiral cuff with multiple contacts and a single lead may be used in place of several muscle-based electrodes each with its own separate lead. A typical result is shown in Figure C.3.1

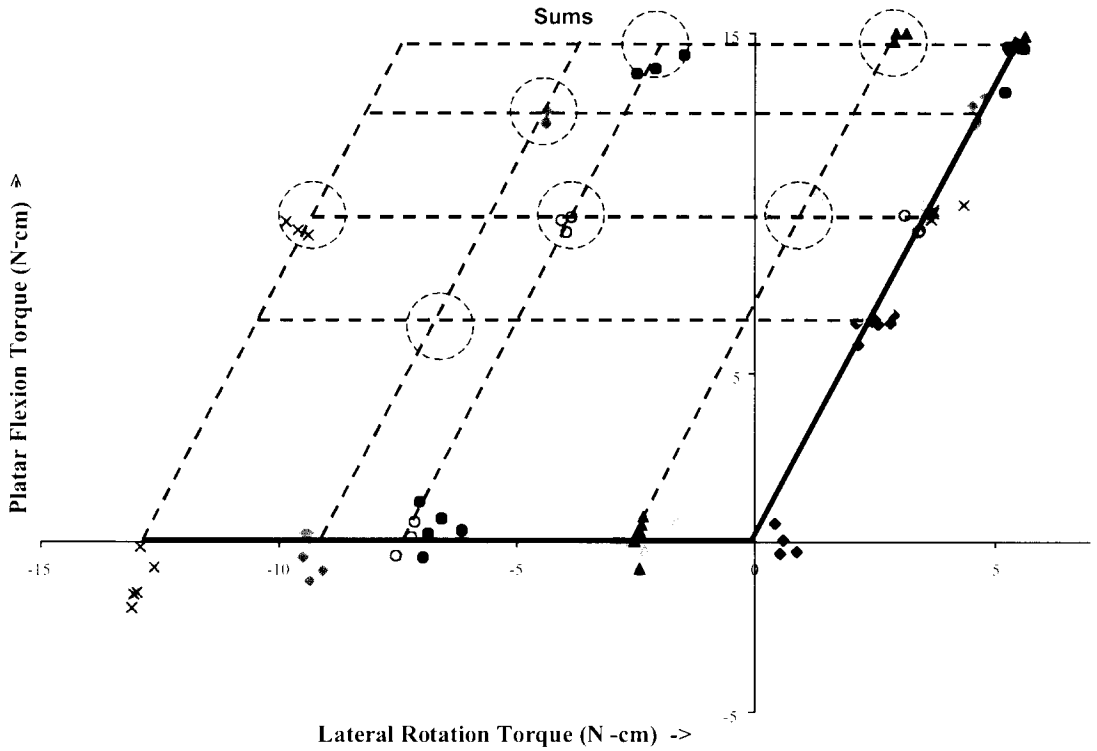


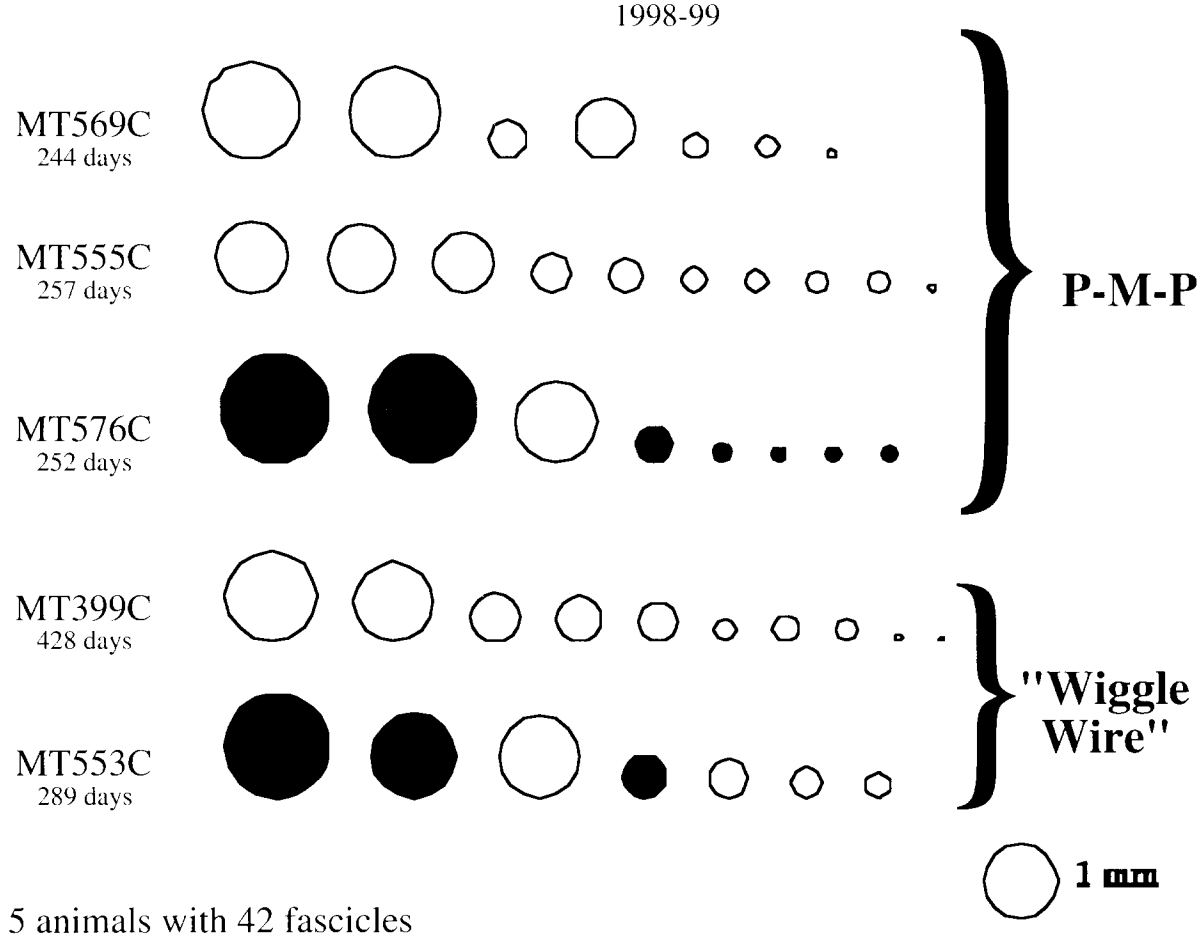
Figure C.3.1 – In this graph is shown an example where two stimuli were applied to effect a linear summation of the torque outputs produced by each individual stimulus. The linear summation was accomplished using a 900μsec delay between the application of the two stimuli. The two solid lines represent the torque output due to application of one stimulus alone. The dashed lines represent the linear summation of the torque produced by each stimulus alone. The seven intersections of two dashed lines that are circled are the predicted torque outputs of the linear summations that were performed. In all 7 cases the average torque output was within the 98% confidence of the predicted linear summation.

C.4 Histopathology of Nerves Having Had Long-Term Implants

Self-sizing spiral cuff electrodes were implanted around the sciatic nerve of five adult cats. The durations of the implants were 244, 252, 257, 289 and 424 days. Two of the cuffs were fabricated using "wiggle wire" fabrication technology and the remaing three were constructed using PMP technology. Cross sections of the implanted nerves were examined with light microscopy. Three of the implanted nerves showed no signs of prior insult and two showed signs of having sustained a prior insult. Signs of having sustained a prior insult were: thinly myelinated axons, increased presence of interneural connective tissues and an apparent decrease in axon density. The results are summarized in the following table.

Summary of Histology from Long-Term Implants on Cat Sciatic Nerve

1998-99



5 animals with 42 fascicles

10/42 = 23% of the fascicles with > 10% of the fibers showing signs of prior insult

2/5 = 40% of the nerves with > 10% of the fibers showing signs of prior insult

zero fibers exhibiting signs of prior insult

less than 10% of the fibers exhibiting signs of prior insult

greater than 10% of the fibers exhibiting signs of prior insult

SECTION D. HUMAN FEASIBILITY TESTING

D.1 Upper Extremity

A proposal has been submitted to support research that will focus on enabling any individual with a cervical level spinal cord injury, regardless of injury level and extent, with the opportunity to gain additional useful function through the use of FNS and complementary surgical techniques. A major focus will be to work on individuals with high tetraplegia (C1-C4), low tetraplegia (C7), and incomplete injuries. Nerve cuff electrodes are more appropriate for activation of the proximal muscles of the upper extremity (elbow and shoulder) than are muscle-based electrodes. These muscles are large, structurally complex, and many have branched innervation. Thus complete activation would likely require multiple muscle-based electrodes. Complete activation is particularly critical in high tetraplegia due to extensive paralysis and denervation. Implantation of muscle-based electrodes would require extensive surgical access to target the wide distribution of muscles. Also, many of the nerves serving the shoulder musculature are located near one another proximally, thereby simplifying surgical installation. Further, some nerves innervate several synergistic muscles, and several muscles can be stimulated at the same time though a single electrode. Finally, the muscles have large excursions due to the large range of motion of the elbow and shoulder joints. Muscle-based electrodes have length-dependent recruitment properties that make control difficult, lead to deadbands and may produce instability. Once encapsulated, nerve cuff electrodes have recruitment properties that change little with limb position.

Many of these characteristics are not true for the more distal hand musculature in the forearm. In this case, activation of distal muscles is sufficient with muscle-based electrodes (epimysial and intramuscular) as has been demonstrated by successful restoration of hand grasp and release using muscle-based electrodes. However, dependent upon the outcome of this application of cuffs, in future applications cuff electrodes may be used for activation of distal muscles, as well.

D.2 Lower Extremity

Prior to implanting cuff electrodes into human volunteers, several key pieces of information are necessary to ascertain their feasibility for use in motor system neuroprostheses for limb movement, such as hip and knee extension for standing and walking applications of electrical stimulation. Currently our colleagues are pursuing quantitative anatomical studies designed to:

1. To establish the feasibility of deploying cuff electrodes in advanced FES systems by documenting the innervation patterns of the quadriceps and gluteal muscles in the lower extremities in a series of cadaveric dissections.
2. To ascertain design parameters for custom-fabricated nerve cuffs appropriate for the femoral and gluteal nerves in the lower extremities by determining their branch-free lengths and diameters in a series of cadaver specimens.
3. To develop practical operative routes, surgical techniques and specialized tools for implanting nerve cuff electrodes with minimal trauma and establish implementation strategies for advanced neuroprostheses.

The first approach is to investigate the possibility of deploying monopolar stimulating cuffs on the major nerve branch innervating a single lower extremity muscle. Based on the results of our anatomical studies, we will determine if a more sophisticated monopolar stimulating cuff with field steering for selective fascicular activation is necessary.

Sufficient knee and hip extension are critical to standing and stepping with FES. Yet, currently available muscle-based electrodes can not always provide adequate muscle forces and

joint moments to extend the knees and hips sufficiently to support the body against gravity. The **gluteus maximus** is a key muscle for extending the hip in lower extremity FES applications because of its size and force generating capacity. This large muscle is innervated by the **inferior gluteal nerve** which exits the pelvis through the lower half of the greater sciatic foramen. The nerve divides into at least two main branches, each of which further sub-divides before penetrating the deep surface of the muscle as separate bundles of nerves. Because of its bulk and pattern of innervation, electrodes placed in (intramuscular) or on the gluteus maximus itself (epimysial) recruit only a portion of the muscle and produce only a fraction of its potential force. The proximity of the inferior gluteal nerve to the sciatic nerve can compromise the selectivity of electrodes in the gluteal region and further complicate the production of strong hip extension. A cuff electrode on the inferior gluteal nerve would obviate these problems by activating the entirety of the muscle and improve performance of neuroprosthetic systems for standing. The quadriceps are responsible for knee extension and consist of four muscles with separate origins joined at the common insertion of the patella tendon. Three heads of the quadriceps are pure knee extensors (the **vastus lateralis**, **vastus medialis** and **vastus intermedius**). The fourth (the **rectus femoris**) crosses both the hip and the knee. A single muscle-based electrode can activate only one of the four muscles, resulting in much less knee extension than physiologically possible. The **femoral nerve** supplies all four quadriceps, as well as the flexors of the hip (the sartorius, tensor fascia lattae and iliopsoas). A nerve cuff electrode located on the femoral nerve to selectively activate all the fibers of the three vasti and avoid the other hip flexors would maximize knee extension without compromising posture by actively flexing the hip. This would result in extended standing time for individuals who may be too heavy to stand safely on one vasti alone.

The first of a series of five quantitative anatomical dissections of the femoral and inferior gluteal nerves in embalmed cadaver specimens have been completed. The general locations of the nerves in the lower extremities are identified and related to bony landmarks and surface anatomy. After removing the skin and subcutaneous fat in the regions of interest, the fibers of the target muscles are split carefully so as not to disrupt their nerve supplies. The nerves of interest are then identified and their major branches released from connective tissue. The nerve branches are traced to the muscle fibers on which they terminate and their respective domains in the muscle will be noted. At this time, the lengths and circumferences of each branch of the nerve will be measured and recorded for later analysis. Morphological measurements of nerve branch-free lengths and circumferences are being obtained as well as the locations and lengths of branch-free segments that may be sufficient for placement of nerve cuff electrodes. Branching patterns and curvature of the nerves as they runs their course are also being noted. These measurements will serve as guidelines for the manufacture of appropriate nerve cuffs, and define a strategy (monopolar or multicontact) for most effective utilization of nerve cuff electrodes.

Preliminary measurements indicate that several potential sites exist for a nerve cuff electrode. The variability of these measurements, and the relative percentages of the muscle fibers innervated by each branch, need to be determined in a larger number of specimens before proposing application in human volunteers. The three dimensional coordinates of the branch-free lengths under consideration for cuff electrode application are being determined with respect to bony landmarks of the pelvis , femur and lumbosacral spine. The innervation patterns for each target muscle from all specimens will be compiled and analyzed for statistically for consistency. If the nerves exhibit a consistent branching pattern and domain of muscle fibers from specimen to specimen, they will be evaluated as candidate locations for nerve cuff electrodes, and used to predict the outcome of placing a cuff electrode on a particular branch of the nerve.

SECTION E. FABRICATION AND DELIVERY OF COMPLETED ELECTRODES

Fifteen self-sizing spiral cuff electrodes were fabricated using PMP technology. Fourteen were delivered to investigators at Case Western Reserve University who are working on upper an lower extremity motor prostheses. One was delivered to Dr. Heetderks, Director to the NIH Neural Prosthesis Program.